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(54) Title: A PROCESS FOR THE PREPARATION OF CIS-(1S,4S)-N-METHYL-4-(3,4-DICHLOROPHENYL)-1,2,3,4-TETRAHYDRO-1-NAPHTHALENEAMINE HYDROCHLORIDE

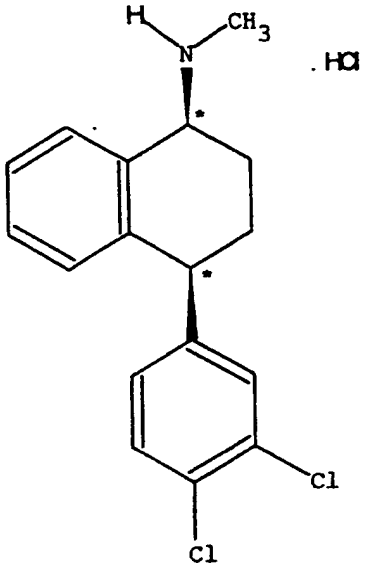
(57) Abstract: There is disclosed a process for the preparation of cis-(1S,4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride i.e. sertraline hydrochloride and the intermediate cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride, which comprises reacting 4-(3,4-dichlorophenyl)-3,4-dihydro-1-(2H)-naphthalenone with methylamine under reducing atmosphere in presence of reducing metal catalyst such as Raney Nickel to produce the intermediate amine, treating the said amine with hydrogen chloride to produce the corresponding cis and trans amine hydrochloride, isolating and purifying the said amine hydrochloride to obtain the intermediate cis-amine hydrochloride, and converting the said cis-amine hydrochloride into cis-(1S,4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride, by known process.

A PROCESS FOR THE PREPARATION OF CIS-(1S,4S)-N-METHYL-4-(3,4-DICHLOROPHENYL)-1,2,3,4-TETRAHYDRO-1-NAPHTHALENEAMINE HYDROCHLORIDE

FIELD OF THE INVENTION

This invention relates to a process for the preparation of N-methyl-4-(3,4-dichlorophenyl)- 1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride and isolation of cis isomers therefrom to synthesize sertraline hydrochloride which is cis-(1S,4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride.

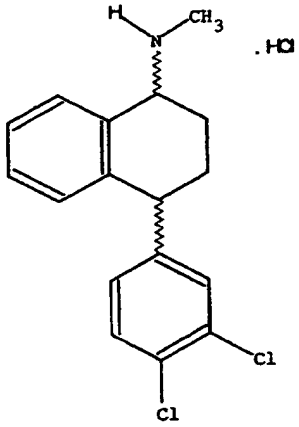
The need for the drugs which lack the obstrusive and limiting side effects of the tricyclic antidepressants had prompted the search for agents with greatly enhanced selectivity for specific mechanisms of actions believed to be essential for antidepressant efficacy. Researches targeted for selective competitive inhibitors of synaptosomal serotonin re-uptake, which led to series of 1-methylamine-4-aryltetralins, of which the most promising was the 4-(3,4-dichlorophenyl) analogue. Testing of all possible stereoisomers revealed that the required high selectivity for serotonin resides in the cis-1S,4S isomer i.e. cis-(1S, 4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride (I) commonly known as sertraline hydrochloride.



(I)

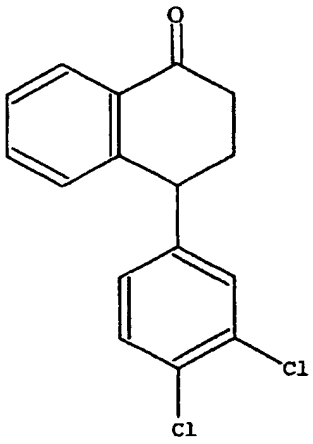
BACKGROUND OF THE INVENTION

Various methods to obtain the isomeric mixture of the key intermediate N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene amine hydrochloride (II) are known in the literature.



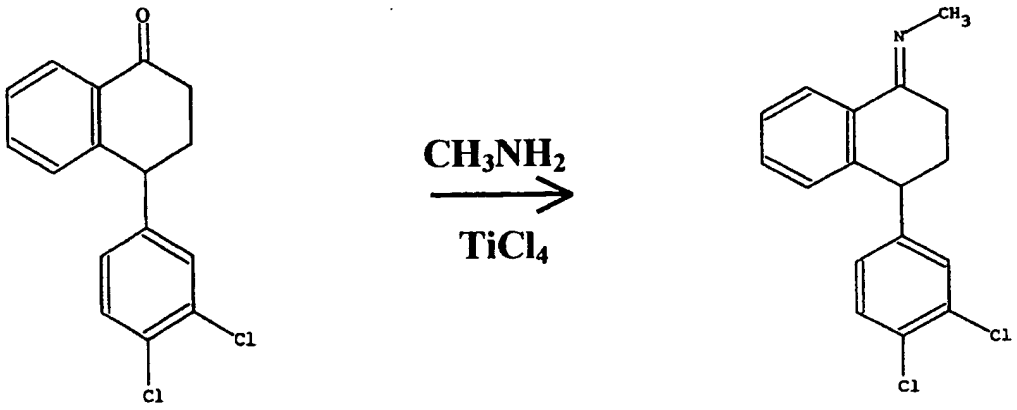
(II)

According to European Patent 0030081 A1, first the carbocyclic framework of 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone (III) was constructed.



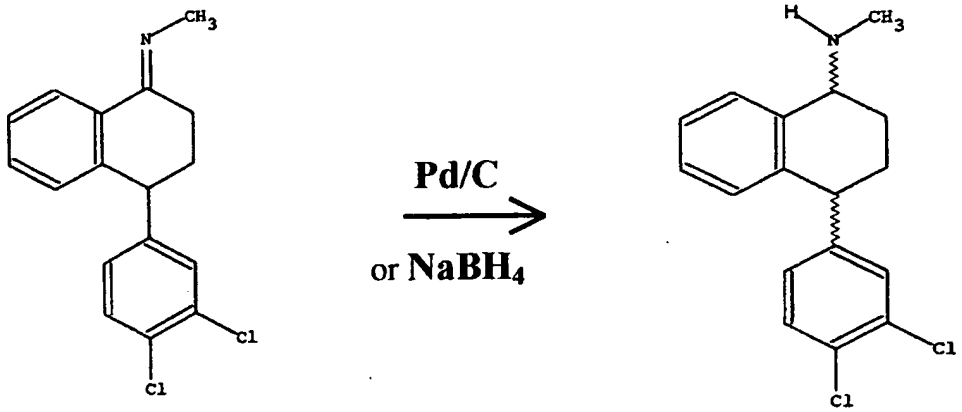
(III)

Conversion of ketone (III) into C_1-imine (IV) was carried out by using methylamine in presence of titanium tetrachloride.



(III) (IV)

The imine was hydrogenated using 10% Pd/C as catalyst to give the corresponding amine (V). Amine was isolated as its hydrochloride salt (II). It is further known in the literature that reduction of C_1-imine (IV) may also be carried out by using a metal hydride reagent e.g. sodium borohydride.



(IV) (V)

The step for conversion of ketone (III) into amine, involving use of titanium tetrachloride is crucial, as the reagent is moisture sensitive and lachrymatory. Also, the next step for hydrogenation involves uses of costlier reagent (Pd/C). In the alternative hydrogenation step, by use of sodium borohydride as reducing agent, the separation of geometrically pure isomer is laborious as well as poor yielding (23%).

SUMMARY OF THE INVENTION

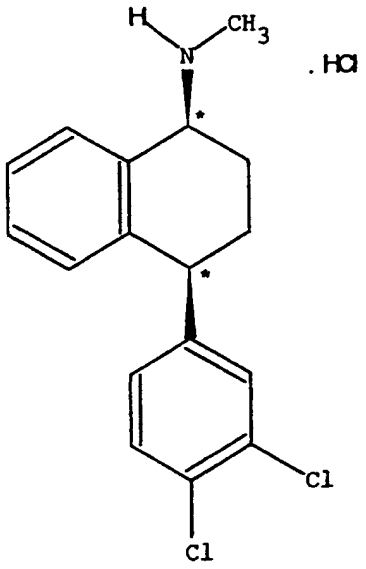
The first object of the invention is to produce sertraline hydrochloride (cis-(1S,4S)-N-methyl-4-(3,4-dichlerophenyl)-1,2,3.4-tetrahydro-1-naphthaleneamine hydrochloride) by a novel, cost effective process.

Another object of the present invention is to produce cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride (intermediate for the preparation of sertraline hydrochloride) via direct reduction process.

Yet another object of the present invention is to produce the said intermediate for production of sertraline hydrochloride in a cost effective manner.

Further object of the present invention is to produce the said intermediate for production of sertraline hydrochloride without the use of titanium tetrachloride and sodium borohydride or Pd/C as reducing agent.

Accordingly, the present invention provides a process for preparation of cis-(1S,4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride i.e. sertraline hydrochloride of the formula I, used extensively as a selective serotonin uptake inhibitor in therapy,

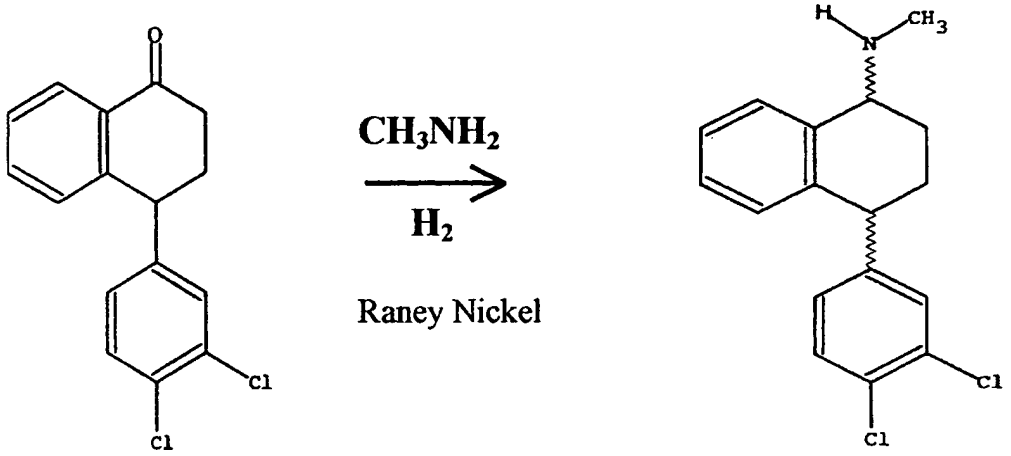


(I)

which comprises the steps of :

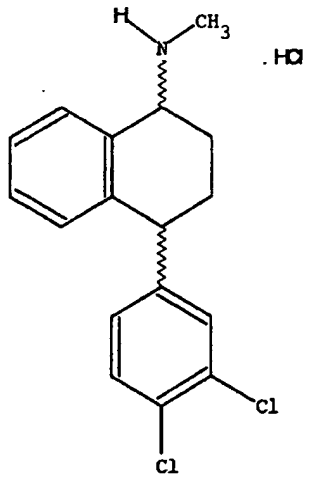
a) reacting 4-(3,4-dichlorophenyl)-3,4-dihydro-1-(2H)-naphthalenone of formula - III

with methylamine under reducing atmosphere in presence of reducing metal catalyst such as Raney Nickel to produce the compound of formula - V



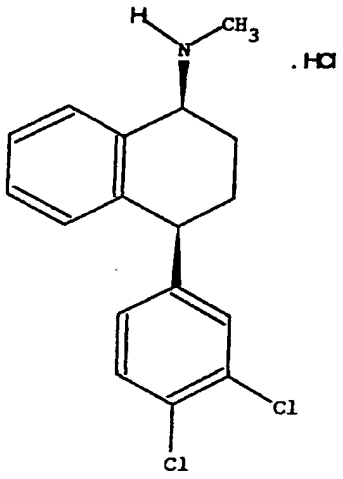
(III) (V)

b) treating the said compound of formula - V with hydrogen chloride to produce the compound of formula - II in 48-51% yield,



(II)

c) isolating and purifying the compound of formula-II to obtain cis-hydrochloride of formula - VI, and



(VI)

d) converting the said compound of formula VI into cis-(1S,4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride of formula (I) by using known process.

The invention also provides for preparation of intermediate cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenemaine hydrochloride of formula - VI, which comprises the process steps (a), (b) and (c) above.

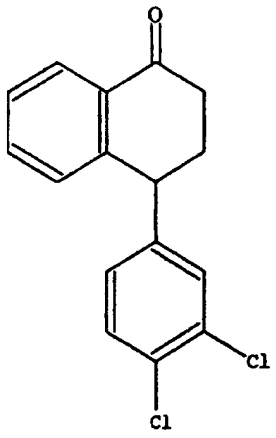
DETAILED DESCRIPTION OF THE INVENTION

The applicant has developed a convenient method of conversion of 4-(3,4-dichlorophenyl)-3,4-dihydro-1-(2H)naphthalenone(III) to amine in single step and amine is isolated as N-methyl-(3,4-dichlorophenyl)-

1,2,3,4-tetrahydro-1-naphthalene amine hydrochloride(II), which is the key intermediate in the synthesis of sertraline hydrochloride(I).

Considering the importance of sertraline hydrochloride (I) as an antidepressant and the need for the improvement in the synthetic process for its production, the applicant has developed a method of synthesis of the key intermediate isomeric N-methyl- (3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene amine hydrochloride (II) for production of sertraline hydrochloride as discussed below :

In the present process reductive amination of C_1-carbonyl to C_1-amine is carried out. 4-(3,4-dichlorophenyl)-3,4-dihydro-1-(2H) naphthalenone (III) and methyl amine are reacted in hydrogen atmosphere in the presence of Raney Nickel as catalyst.

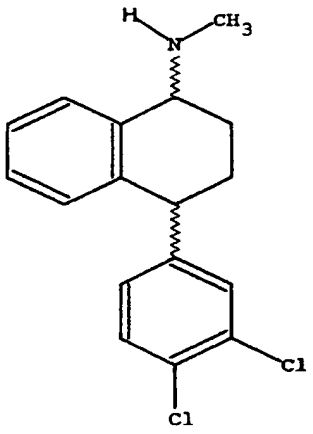


(III)

CH_3NH_2

H_2

Raney Nickel



(V)

Solvent for the reaction is protic polar in the nature. Protic polar solvent, for example, lower alcohol such as C_1-C_3 alcohols may be used. In an autoclave carbonyl compound is added followed by methylamine taken in the solvent. Freshly prepared Raney Nickel (W2) is used as reductive amination catalyst.

Reaction is carried out under different hydrogen pressures ranging from 200-1000 psi. Also, the temperature as one of the preferred parameters, may be varied over the range of room temperature to 100°C. Preferred solvent is methanol. Preferred hydrogen pressure is 450-500 psi and preferred temperature is 60°C. Reductive amination is carried out for 15 to 20 hrs. to give (V), a mixture of cis and trans isomers of N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine. Amine (V) is isolated as its hydrochloride salt (VI) via (II). As would be evident from formula II that it has two chiral centres, so several geometric and stereoisomers are possible. The applicant's point of interest is cis-(1S,4S) isomer, used as a drug, as discussed above.

This is achieved by evaporating 50-60% of methanol from the reaction mixture of the reduction process to give amine (V) and the amine, so produced, is further converted to its hydrochloride salt (II) by using hydrochloric acid at 5-10°C to obtain cis-hydrochloride (VI) in 48-51% yield, followed by its conversion into sertraline hydrochloride.

Preferably the isolation of cis-isomer and its conversion to cis-(1S,4S) isomer is carried out by separating all cis-isomers from the said isomeric compound of formula II through selective crystallisation in methanol as solvent, followed by resolution of said separated cis-isomers by known method with mandelic acid, isopropyl alcohol and hydrogen chloride to yield the desired cis-(1S,4S) isomer.

PREPARATORY EXAMPLES

1. **Preparation of isomeric mixture of cis and trans N-methyl 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride and separation of cis isomers therefrom** :

In an autoclave 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone (15.0 gm) is taken, followed by addition of 250 ml. solution of methylamine in methanol (14.5% w/v). To the above solution 3.75 gm. of Raney Nickel (freshly prepared) is added carefully. The autoclave is kept under 450-500 psi of hydrogen pressure. Reaction mixture is heated to 60°C with stirring for 16 hrs. After filtration the filterate is concentrated under reduced pressure to the final volume of 125 ml. It is then acidified to pH 2.5 at 10°C by HCl gas while maintaining the temperature to get isomeric mixture of cis and trans forms. This solution is then heated to 50-55°C for 0.5 hr and finally cooled to 5°C to give 48-51% yield of the cis-isomers.

2. **Preparation of cis-(1S,4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride.**

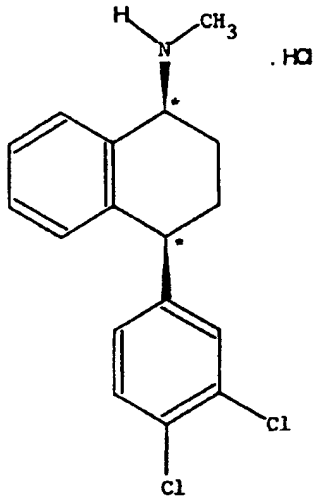
As per the procedure described in Welch W.M.etal. J.Med.Chem, 1984, 27, 1508-1515 racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride (67.1g) was partitioned between 20% aqueous NaOH and ethyl acetate, followed by drying of the organic layer and evaporation to yield the cis-racemate free base (60.2g, 0.197 mol). This oil was dissolved in absolute ethanol (600 ml) and treated with D-(-)-mandelic acid (29.94g, 0.197 mol). The resulting mixture was warmed on a steam bath to effect solution and then held overnight at room temperature to afford a white crystalline solid. This solid was separated by filtration, washed with ether and air-dried (38.7g, mp 188-189°C) and was then recrystallized from hot absolute ethanol to give 32.6 g of solid, mp 190-191°C. An additional crop (4.4 g, mp 190-191°C) was obtained by evaporation of the mother liquors under vacuum followed by crystallization of the residues from boiling ethanol (150 mL).

As per the procedure described in US 5,248,699 (1993) to a 500 ml. 3-neck RB flask equipped with mechanical stirrer, 43 ml. of methylene chloride, 26 ml. water and 6.38 gms. sertraline mandelate were combined. A 10% sodium hyroxide solution, 3.83 ml., was then added

and the resulting two clear layers were separated. The aqueous layer was further extracted with 2 x 6 ml. of methylene chloride. The combined methylene chloride layers were washed with 2 x 12 ml. water and separated. The methylene chloride solution was atmospherically distilled and displaced with isopropanol to a final volume of 45 ml. and 0.5 ml. water was added to the resulting isopropanol solution. The solution was cooled to 50°C and seeded with sertraline hydrochloride. 2.1 ml. of 6.37 molar hydrogen chloride, in aqueous isopropanol was added to the clear solution to give a thick white slurry. Additional isopropanol 15 ml. was added and the material stirred for three hours at 50°C, then cooled to room temperature overnight. The solution was distilled at atmospheric pressure to remove 19 ml. Isopropanol (10 ml.) was then added. The mixture was then cooled and filtered to yield desired crystalline polymorph.

I CLAIM :

1. A process for the preparation of cis-(1S,4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride i.e. sertraline hydrochloride of the formula I, used extensively as a selective serotonin uptake inhibitor in therapy

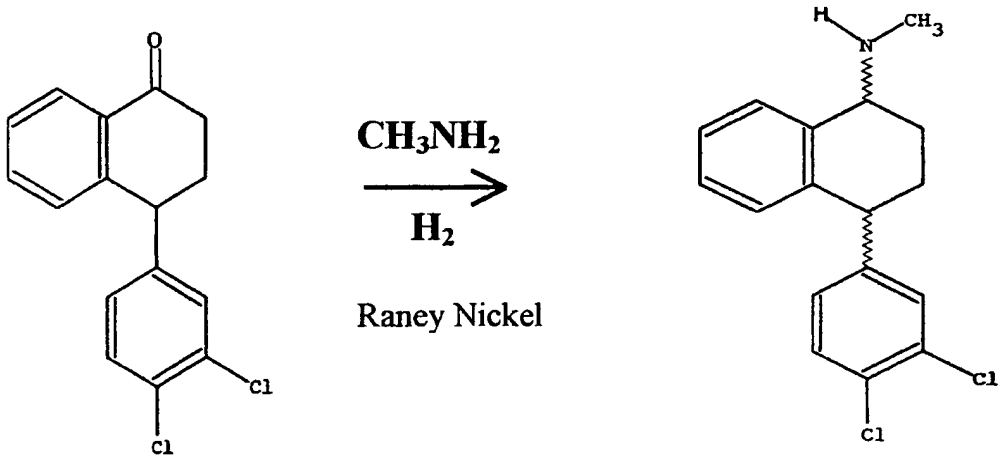


(I)

which comprises the steps of :

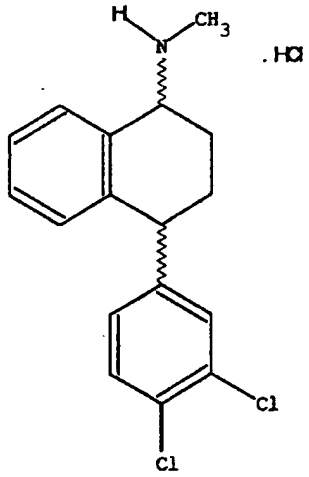
a) reacting 4-(3,4-dichlorophenyl)-3,4-dihydro-1-(2H)-naphthalenone of formula - III

with methylamine under reducing atmosphere in presence of reducing metal catalyst such as Raney Nickel to produce the compound of formula - V



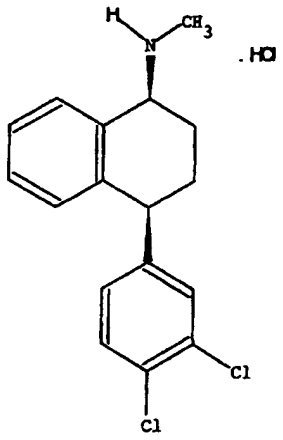
(III) (V)

b) treating the said compound of formula - V with hydrogen chloride to produce the compound of formula - II in 48-51% yield,



(II)

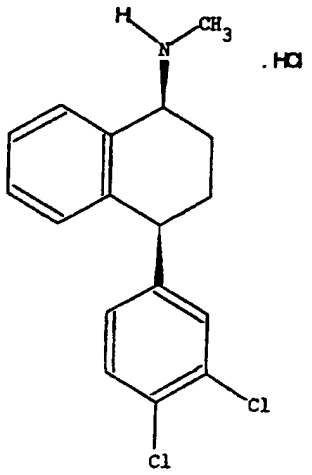
c) isolating and purifying the compound of formula-II to obtain cis-hydrochloride of formula - VI, and



(VI)

d) converting the said compound of formula VI into cis-(1S,4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride of formula (I) by using known process.

2. A process for the preparation of cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenemaine hydrochloride of formula - VI,

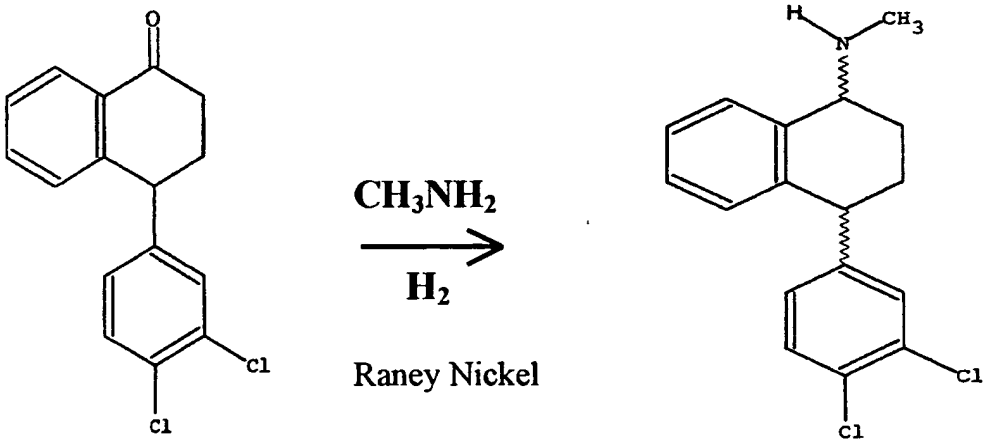


(VI)

which is a crucial intermediate for the production of Sertraline hydrochloride,

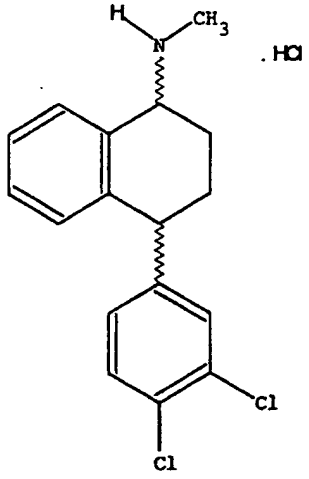
which comprises the steps of :

a) reacting 4-(3,4-dichlorophenyl)-3,4-dihydro-1-(2H)-naphthalenone of formula - III with methylamine under reducing atmosphere in presence of reducing metal catalyst such as Raney Nickel to produce the compound of formula - V,



(III) (V)

b) treating the said compound of formula - V with hydrogen chloride to produce the compound of formula - II in 48-51% yield,



(II)

c) isolating and purifying the compound of formula-II to obtain cis-hydrochloride of formula - VI.

3. A process as claimed in claim 1 or 2 where in said methyl amine is methanolic methyl amine.

4. A process as claimed in any preceding claim, wherein said reaction of naphthalenone with methyl amine is carried out at a temperature range from room temperature to 100°C.

5. A process as claimed in claim 4, wherein the reaction is carried out at 60°C.

6. A process as claimed in any preceding claims, wherein said reducing atmosphere for reaction of naphthalenone with methyl amine is pressurized hydrogen atmosphere.

7. A process as claimed in claim 6, wherein the said reaction is carried out under hydrogen pressure in a range from 200 to 1000 psi.

8. A process as claimed in claim 7, wherein the hydrogen pressure is 450 to 500 psi.

9. A process as claimed in any preceding claims, wherein a protic polar solvent is used for reaction of naphthalenone with methyl amine.

10. A process as claimed in claim 9, wherein the solvent is lower alcohol such as C_1-C_3 alcohols.

11. A process as claimed in claim 10, wherein the solvent is methanol.

12. A process as claimed in claim 1, wherein said isolation and conversion steps comprises the steps of separating all cis-isomers from the said isomeric compound of formula-II through selective crystallisation in methanol as solvent, followed by resolution of said separated cis-isomers by known method with mandelic acid, isopropyl alcohol and hydrogen chloride to yield the desired cis(1S,4S)isomer.

INTERNATIONAL SEARCH REPORT

Interna ıl Application No
PCT/IB 00/01182

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C209/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 36394 A (COLBERG JUAN CARLOS ;PFISTERER DAVID MICHAEL (US); PFIZER PROD INC) 22 July 1999 (1999-07-22) page 5, line 7 - line 12 page 6-9 page 15 -page 16; example 6 ---	1-12
A	EP 0 030 081 A (PFIZER) 10 June 1981 (1981-06-10) cited in the application page 17, line 26 -page 20, line 16 -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
6 December 2000	18/12/2000

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...rmation on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9936394 A	22-07-1999	AU 9278698 A	02-08-1999
		BR 9814248 A	10-10-2000
		EP 1047666 A	02-11-2000
		NO 20003625 A	13-09-2000
EP 0030081 A	10-06-1981	US 4536518 A	20-08-1985
		AT 2668 T	15-03-1986
		AU 517357 B	23-07-1981
		AU 6389780 A	07-05-1981
		BA 97149 B	28-12-1998
		BA 97150 B	28-12-1998
		BG 60333 B	27-05-1994
		CA 1130815 A	31-08-1982
		CS 9103542 A	16-12-1992
		CS 238609 B	16-12-1985
		CS 238617 B	16-12-1985
		CS 238618 B	16-12-1985
		DD 155615 A	23-06-1982
		DD 203045 A	12-10-1983
		DE 3062225 D	07-04-1983
		DK 395280 A,B,	02-05-1981
		EG 15527 A	30-04-1987
		ES 496443 D	16-01-1982
		ES 8201949 A	01-04-1982
		ES 506892 D	01-09-1982
		ES 8207123 A	01-12-1982
		FI 803398 A,B,	02-05-1981
		GR 70781 A	23-03-1983
		HK 82284 A	09-11-1984
		HR 930199 B	29-02-1996
		HR 931527 B	30-04-1996
		HU 182224 B	28-12-1983
		IE 50395 B	16-04-1986
		IL 61374 A	31-10-1983
		IN 159644 A	30-05-1987
		IN 159643 A	30-05-1987
		JP 1287061 C	31-10-1985
		JP 56086137 A	13-07-1981
		JP 60005584 B	12-02-1985
		KR 8402001 B	27-10-1984
		KR 8402000 B	27-10-1984
		LU 88330 A	04-05-1994
		LV 5456 A	10-03-1994
		LV 5457 A	10-03-1994
		MX 5980 E	12-09-1984
		MY 32685 A	31-12-1985
		NO 803258 A,B,	04-05-1981
		NZ 195407 A	31-05-1984
		PH 17319 A	20-07-1984
		PT 72004 A,B	01-11-1980
		SG 56584 G	08-03-1985
		SI 8012798 A	31-12-1994
		SI 8310672 A	30-04-1996
		SU 1014467 A	23-04-1983
		SU 1034602 A	07-08-1983